REMARKS

Claims 1-9 are pending in the present application. New page 1 of the drawing page includess new Fig. 2, which has been corrected as required by the Examiner to indicate that the figure refers to a prior art diversion valve. The correction is supported at page 5, lines 9-10, of the specification.

Claims 1-4 and 9 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,508,204 to Norman (hereinafter "the Norman patent"). Applicant respectfully requests reconsideration. The Norman patent describes a method for sequential and serial introduction of samples containing a single target analyte. The Norman patent does not disclose or suggest the possibility of simultaneous injection of samples containing the same or different target analytes as in the present invention.

The method disclosed by the Norman patent is only useful if a single analyte can be distinguished from background interferences that might coelute with the target analyte. While this may be useful for certain select analytes, such as methylmalonic acid in urine, the method cannot be applied to the measurement of multiple analytes at low levels in the presence of background interferences.

The Norman patent requires that the multiple injections of the samples result in a series of peaks for the target analyte that are chromatographically separated from each other and from background interferences. The analyte mass that is measured by the mass spectrometer must be unique; therefore, the method described in the Nonnan patent will fail if coeluting background interferences (similar compounds, isomers, etc.) are present that have the same mass as the target analyte. The likelihood of such coeluting interferences is greatly increased by injecting multiple samples onto the chromatographic column during a single analysis period. Later injections will be more likely to suffer such interference.

Further, the method disclosed in the Norman patent is not effective for the analysis of different analytes, such as those analyzed for by combinatorial chemistry methods. The problems of analyte specificity described above become prohibitive if different analytes are analyzed.

Lastly, the Norman patent describes a quantitative analysis method for a known target analyte. It cannot be used for the qualitative or quantitative analysis of unknown analytes.

The method disclosed by the Norman patent is limited in the following ways:

1. limited to serial quantitative measurement of single known target analytes;
2. cannot be used for simultaneous sample injections;
3. is unsuited for the determination of unknown analytes;
4. is limited in application by problems arising from coeluting background interferences that cannot be distinguished from the target analyte; and
5. cannot be used with multiple chromatographic inlets.

The present patent application describes and claims the application of simultaneous sampling of multiple known or unknown analytes and provides a solution to the limitations described above. Unlike the Norman patent, Applicant's claimed method is directed to simultaneous sample introduction rather than sequential sample introduction. It can be used for the qualitative and quantitative analysis of both known and unknown samples. It can be used for single or multiple chromatographic inlets.

As the Norman patent does not disclose, suggest, or provide any motivation for the simultaneous injection of samples containing the same or different target analytes, the Applicant's claimed method is not obvious over the Norman patent. Therefore, the rejection of claims 1-4 and 9 under 35 U.S.C. § 103(a) should be withdrawn.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being obvious over the Norman patent in view of U.S. Patent No. 4,978,852 to Williams et al. (hereinafter "the Williams patent"). Applicant respectfully requests reconsideration.

The Williams patent describes a Hadamard transform method for simultaneous sample analysis. However, the Williams patent is specifically limited to a particular technique in mass spectrometry, specifically "tandem and multidimensional mass spectrometry" (also known as MS/MS or MS^n). The Williams patent describes a means for obtaining product-ion mass spectra from multiple precursor ions. The Williams patent is limited as follows:

1. limited to mass spectrometry and only tandem mass spectrometry;
2. does not provide a means for detecting single-stage mass spectra;
3. it is impractical or impossible for use with mass analyzers other than Fourier transform or ion trap mass spectrometers;
4. not practical for use with rapid sample introduction from a chromatographic inlet;
5. cannot be used with multiple chromatographic inlets; and
6. cannot be used with spectroscopic methods other than mass spectrometry.

Unlike the Williams patent, the Applicant's claimed method is not limited to tandem mass spectrometry. The Applicant's method is compatible with various forms of spectroscopy, including single-stage, tandem, and multi-stage mass spectrometry. It is also compatible with rapid chromatography and provides advantages over existing methods for combining multiple chromatographic inlets and high-speed chromatography with mass spectrometric analysis.

No combination of the Norman patent and the Williams patent discloses, suggests, or provides any motivation for the simultaneous injection of samples containing the

same or different target analytes in a single analyzing instrument followed by mathematically deconvoluting the results to produce analyses corresponding to individual fluid specimens as in the present invention. Therefore, the rejection of claim 4 under 35 U.S.C. § 103(a) should be withdrawn.

Claims 6-8 stand rejected under 35 U.S.C. § 103(a) as being obvious over the Norman patent in view of U.S. Patent No. 6,066,848 to Kassel et al. (hereinafter "the Kassel patent"). Applicant respectfully requests reconsideration.

The Kassel patent discloses a means for using a single mass spectrometer together with multiple chromatographic inlets. The Kassel patent does not recognize the possibility of introducing samples in linearly independent combinations. The Kassel patent specifically states throughout the text that the blocking device is positioned "to block all but one" of the fluid samples, and that the fluid samples are introduced "one at a time" (col. 2, lines 41-47, for example). The number of separate fluid streams that can be measured by this method is limited by the chromatographic peak width. That is, the sampling time for each fluid stream must be significantly faster than the typical chromatographic peak width in order to ensure that each analyte is sampled as it elutes from the chromatographic column.

Specifically, the Kassel patent is limited as follows:

1. limited to sampling one fluid stream at a time;
2. does not consider the possibility of enhanced signal-to-noise ratio or more rapid data acquisition through simultaneous sampling in linearly independent combination; and
3. limited in terms of the number of fluid streams that can be sampled for a given chromatographic peak width.

Unlike the Kassel patent, the Applicant's claimed method makes use of simultaneous sample introduction and does not introduce one fluid stream at a time. It provides a distinct advantage over the Kassel patent in the case where the chromatographic peak is narrow and one wishes to sample a number of chromatographic inlets (as shown in Fig. 1).

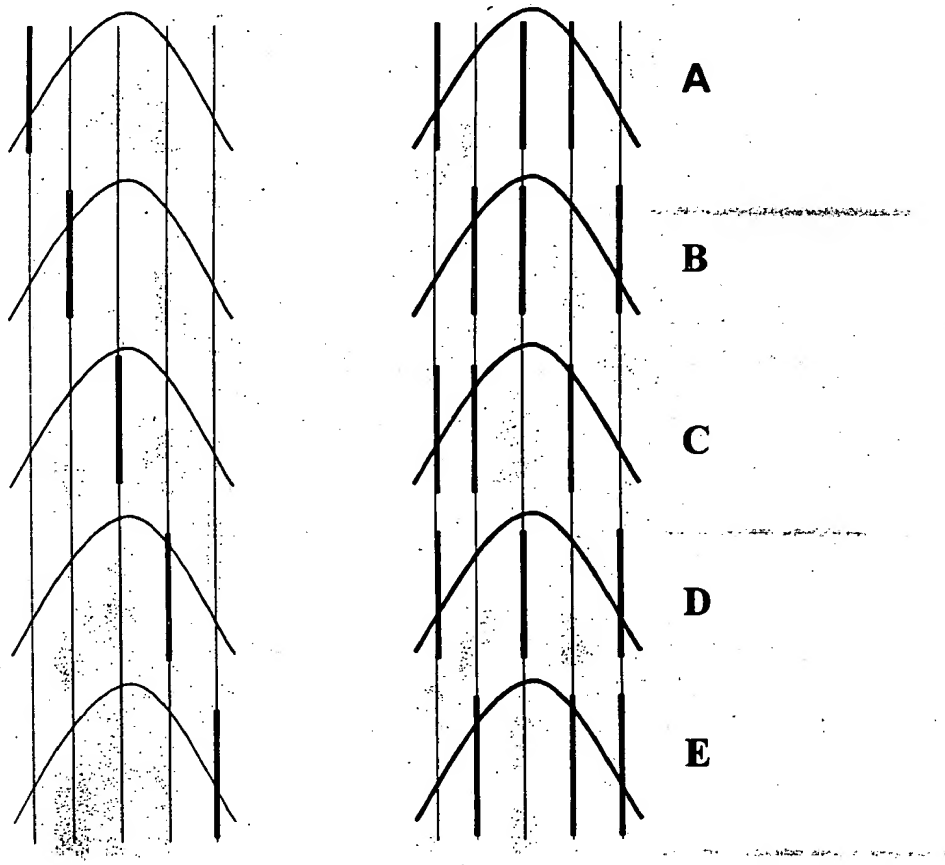

Fig. 1- Comparison of one at a time sampling (left, as in the Kassel patent) with multiplexed sampling (right, as in the present invention) for five compounds.

The methodology of the Applicant's method has specific benefits if one wishes to multiplex samples that vary in time. For example, consider that we wish to multiplex five input streams where five analytes (labeled A, B, C, D, E) elute over the same five-second period. Present "one-at-a-time" sampling methods will only sample each analyte only one time during

the elution. As shown in Fig. 1, analytes A and E will produce very small signals because they are measured at the start and end of their elution period. If the sampling occurs slightly earlier or later, the analytes may not be detected at all. In contrast, sample C will produce a very strong signal, and samples B and D will produce an intermediate signal. The Applicant's method samples each analyte three times during the elution period, producing a more uniform signal and better signal-to-noise ratios for all analytes.

Unlike the Norman or Kassel patents, the Applicant's method provides an improved signal-to-noise ratio and describes a method for reducing or eliminating a constant chemical background.

Contrary to the Examiner's assertion, the method described in the Applicant's claims would not have been obvious to one of ordinary skill in the art. A device nearly identical to that described by Kassel has been commercially available from MicroMass for several years. During that time, no one has proposed, attempted, or demonstrated the method described in the present claims, despite the inherent advantages. No combination of the Norman patent and the Kassel patent discloses, suggests, or provides any motivation for the simultaneous injection of samples containing the same or different target analytes in a single analyzing instrument as in the present invention. "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In re Napier, 55 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996). "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1399 (Fed. Cir. 1989). Therefore, the rejection of claims 6-8 under 35 U.S.C. § 103(a) should be withdrawn.

In view of the above amendments and remarks, reconsideration of the rejections and allowance of claims 1-9 are respectfully requested.

Respectfully submitted,

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